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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 28 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Terbutryn (NRDC) Chemical

FROM: Alex Arce
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Jan 21-86

TO: Paul Parsons, PM 60
Registration Division (TS-767C)

THRU: Clint Skinner, Ph.D.
Head, Section III

1-23-86

and

Theodore Farber, Ph.D., Chief
Toxicology Branch (TS-769C)

Compound: Terbutryn

EPA ID # 080813

Tox. Chemical No.: 125D

Accession Nos.: 259886 and 259887

Registrant: Ciba-Geigy

Record No.: 161855

Action Requested:

Review of teratology data; rat and rabbit, terbutryn is an NRDC Chemical and Registration Standard.

Recommendation or Conclusion:

The two studies are acceptable. Refer to one-liner (attached) for results.

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Background Information:

These studies are submitted for the Registration Standard: the rat study is submitted to replace a previous one that was conducted "Not in accordance with EPA Guidelines."

Information Submitted:

Two studies: rat and rabbit teratology.

Discussion:

The studies are acceptable to establish that terbutryn as tested using rabbits is not a teratogenic product and does not induce fetotoxicity. The only adverse effect was a reduction in food consumption of the mothers observed at each one of the dose levels. The rat study establishes that the product is not a teratogenic agent but induces developmental changes, maternal and fetal toxicity.

DATA EVALUATION REPORT

Chemical: Terbutryn

Test Material: Terbutryn Technical

Study Type: Teratology Report No. 85010

Title: A Teratology Study in New Zealand White Rabbits (MIN 842105)

Laboratory: Ciba-Geigy Pharamaceutical Division, Reproductive and Genetic Toxicology Subdivision

Location: Summit, NJ 07901 Date: October 1, 1985

Lab. No.: Ref. No. I-023-02

Sponsor: Agricultural Division of Ciba-Geigy

EPA ID No.: 080813 MRID: None Accession No.: 289886

Reviewed by: Alex Arce Date: January 1986
Toxicologist Phone: 557-7457
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Approved by: Clint Skinner, Ph.D. Date:
Section III Head Phone:
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Conclusion:

Developmental Toxicity

Developmental NOEL = 75 mg/kg (HDT)

A/D ratio 10/75 = 0.13

-Maternal NOEL = 10 mg/kg LEL = 50 mk/kg

Levels tested by gavage in New Zealand White Strain ; 0,10,50 and 75 mg/kg /day
Core Classification: Guideline

Protocol:

Test Material and Methods:

Material: Terbutryn Technical
3% corn starch containing 0.5% Tween 80

Animals: New Zealand White Rabbits

Sex: female; Age: adult; Weight: Acceptable;
Source: Not established.

Dosage: 0, 10, 50 and 75 mg/kg/day
Number of animals per dose level: 19 mothers/dose level

Description:

The product was administered by gavage to pregnant rabbits during the 7th to 19th day of gestation in three dose levels, daily. The rabbits were necropsied on day 29 and mothers of fetuses were examined and weighed. Visceral abnormalities were recorded.

Reported Results: (Refer to attached addendum extrated from submitted data)

Deaths: None

The food consumption and body weight gain in all groups decreased. The product is reported to be not embryotoxic, fetotoxic or teratogenic. Induced loss weight in the mothers at all doses.

Observations:

Signs of Toxicity: Daily

Behavior: Daily

Body Weights: On days 0, 7, 14, 19, 21, 25 and 29.

Food Consumption: Daily from day 0 to day 28.

Examinations:

Laparohysterectomy was performed, livers were weighed. ovaries were examined, corpora lutea counted, dead fetuses and absorptions were counted, the portions of the fetuses in the uterus were recorded. The fetuses were measured and weighed.

Maternal Examinations: (Extrated from Submitted protocol)

All mothers were examined for external and internal gross malformations or pathological changes. Representative samples of gross lesions were collected for microscopic observations.

Fetal Examinations:

(From submitted Data)

Fetal Dissection:

On the day of necropsy (if possible) each fetus was examined viscerally according to a modification of the Staple technique (Staples, R.E., Teratology 9 (3): A-37, 1974) and its sex determined. The visceral examination was conducted on all fetuses as soon as possible following necropsy (not more than 24 hours). Visceral examination includes the following systems, organs and glands which were examined using dissection and slicing under appropriate magnification:

Central Nervous System:	brain
Cardiovascular System:	heart, major blood vessels
Respiratory System:	trachea, lungs, diaphragm
Gastrointestinal System:	oral cavity, tongue, esophagus, stomach, intestines, liver, gallbladder, pancreas
Lymphoid Structures:	thymus, spleen
Urinary System:	kidneys, ureters, bladder
Endocrine System:	adrenals
Genital System:	ovaries, uterus or testicles

Visceral examination data were collected on the standard R&GT visceral collection forms, the results of these data were tabulated manually (Appendix 19A), and the tabulations sent to the Statistics Section for analysis. Results of the visceral exams are recorded as normal or abnormal in the raw data; whereas, only abnormal data are presented and summarized in this report.

The fetuses were then prepared for a subsequent skeletal examination after clearing in potassium hydroxide and staining with Alizarin Red S (Staples and Schnell, Stain Technology 39: 62, 1964). This method is a modification of the method described by Dawson (Dawson, A.B., Stain Technical 1, 1926, p. 123-124).

Skeletal Examination:

Following the visceral examination, all fetuses were stained and subjected to skeletal examination using appropriate magnification. All ossification centers that are characteristically present at day 29 of gestation in this strain of rabbit were examined for: presence/absence, size, shape, location and relationship to adjacent ossification centers. The Reproductive Skeletal and Visceral Program (R.S.V.P.) system an in-house

developed and validated database management system was employed to collect the data from the skeletal evaluations and the printouts generated are the raw data.

Results: (Refer to attached data , extrated from submitted study)

Mortality: None for the mothers (Some does were sacrificed due to conditions not related to treatment)

Signs of toxicity: Variations in the feces at the mid- and high-dose group. Other observations were not related to treatment.

Food consumption: Decrease at the high-dose level during gestation period. The other groups also showed decreases. Such observations were significant even at the lowest treatment dose.

Body weight: Although no significant differences between treated and control mothers were observed, the variations in maternal body weights were significant at various intervals and they were related to the variations in feed consumption.

Pathology: None of the various findings can be related to the administration of the compound.

Reproductive Observations:

No significant findings were observed.

Maternal Parameters:

Viable fetuses, number: normal.

Number of corpora lutes: no significant variations.

Sex of the fetuses: no significant variations.

Weights and Growth: no significant variations.

Number of litters: no significant variations.

Number of pregnant animals: no significant variations.

Number of abortions: not reported.

Fetal Parameters:

Length:

Weight and Growth: no significant differences.

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External observations:

Sex: no significant differences.

Visceral Observations: (Refer to attachment)

The various occurrences observed were noted at random in the three dose levels and the controls; thus they cannot be attributed to the administration of the material.

Skeletal Observations: (Refer to attachment)

The variations noted were regarded as general occurrences in rabbits; thus, not significant.

Alive fetuses: no significant differences. (Refer to attachment)

Dead fetuses: unremarkable.

Discussion:

The report is complete, the study was well designed and conducted. The conclusions are accurate and acceptable. The study is scientifically sound. The biological meaning of the effects reported are that the product is not a teratogenic agent, it does induce developmental changes expressed as reduction in body weights but is not fetotoxic. The mechanism of these effects is related to the toxicity of the material that affected the maternal body weights and food consumption, at random. These effects mean that the material is safe for the intended use, as per this test.

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Pages 8-18 Access to FIFRA Registration Data is restricted under FIFRA section 10(g)

DATA EVALUATION REPORT

Chemical: Terbutryn

Test Material: Terbutryn Technical

Study Type: Teratology

Title: Teratology Study in Rats (MTN 842292)
Report No. 85111

Laboratory: Ciba-Geigy Corporation, Research Department and Genetic Toxicology Subdivision

Location: Summit, NJ Date: October 25, 1985

Lab. No.: Not submitted.

Sponsor: Ciba-Geigy

EPA ID No.: 080813 MRID: None Accession No.: 289887

Reviewed by:

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Approved by: Clint Skinner, Ph.D.
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Date: January 1986
Phone: 557-3710

Conclusion:

Core-Minimum Data (Requires Registrant's explanation)

Developmental Toxicity

NOEL = 50 mg/kg (HDT)
LEL = 500 mg/kg

A/D ratio 10/50 = 0.2

Maternal toxicity NOEL = 10 mg/kg
LEL = 50 mg/kg
(Mortality, weight loss, salivation, urine stain, blood discharge)

Fetal toxicity NOEL = 50 mg/kg (HDT)
LEL = 500 mg/kg

Core Classification: Minimum

were weighed and the fetuses examined for gross abnormalities, then placed into either 95 percent ethanol or Bouin's fixative for subsequent skeletal of visceral examination.

Fetal Examinations:

Approximately 1/3 of the fetuses were fixed in Bouin's solution for at least 1 week and then examined for visceral abnormalities according to the method of Monie, Kho, and Morgan (Supplement to Teratology Workshop Manual, pp. 163-169, 1965).

The visceral examination evaluates the following biological systems, organs and glands which are examined using dissection and slicing (where applicable) techniques under the appropriate magnification:

Central Nervous System:	brain
Cardiovascular System:	heart, and major blood vessels
Respiratory System:	nasal passages, trachea, lungs, diaphragm
Gastrointestinal System:	oral cavity, tongue, esophagus, stomach, intestines, liver, pancreas
Lymphoid Structures:	thymus, spleen
Urinary System:	kidneys, ureters, bladder
Endocrine System:	adrenals
Reproductive System:	ovaries, uterus or testicles

Skeletal Examination:

Approximately 2/3 of the fetuses from each litter were stained with Alizarin Red S and cleared according to the method of Staples and Schnell (Stain Technology 39:62, 1964), and then examined for skeletal abnormalities.

The rodent skeletal examination involves checking, with the aid of appropriate magnification, all ossification centers that are characteristic of a rat fetus on gestational day 20 (Fritz, H. and Hess, R., Teratology, 3, 1972, Walker, D.G. and Wirtschafter, Z.T. The Genesis of the Rat Skeleton, A. Laboratory Atlas, Charles C. Thomas, Springfield, Illinois, 1967). The examination includes checking for the presence/absence, size, shape, location and relationship to adjacent ossification centers.

Results: (Refer to attached data extracted from submitted protocol)

Mortality: Mothers 2/25 found dead on day 20.

Signs of toxicity: Reduction of weight, feed consumption and weight gain, salivation, swollen abdomens, red stains around vulva, anus, face; lethargy and ptosis.

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Behavior: Lethargic., at the high dose level

Body weight: Reduced at the high-dose level. Due to the large dose administered (500 mg/kg) such reported occurrences were expected.

Necropsy: Distended stomachs at the high dose level in most animals

Maternal Parameters:

Viable fetuses, number: significant (refer to conclusion).

Number of corpora lutes: no significant variations.

Sex of the fetuses: no significant effects on sex ratio.

Weights: severe at the high dose group.

Number of litters: no significant variations.

Number of pregnant animals: no significant variations.

Number of abortions: no significant variations.

Fetal Parameters: (Refer to attached data extrated from submitted protocol)

Length: reduced at the high-dose level.

Weight: decreased at the high-dose level.

External Observations: Pups

Weight decreased to 71 percent of controls at the high-dose level.

Visceral Observations: Not significant. (for pups)

Skeletal Observations:

(From Report)

Fetotoxicity, as a consequence of severe maternal toxicity, was only observed in the high-dose group as male and female fetal weights were reduced to 71 percent of control values. This fetal growth retardation was associated with a significant increase in variations (primarily localized to the periphery of the fetal skeleton) including: 1) Bipartite, misaligned, and not ossified, centrum/vertebrae, 2) misaligned and not ossified, sternebrae, 3) metacarpals, proximal phalanges, and distal phalanges not ossified in the forepaw, and 4) metatarsals, distal phalanges, not ossified in the hindpaw. There were no compound-related fetal gross, skeletal and visceral malformations. There were no fetal effects at the low or intermediate-dose level.

Discussion:

There are certain discrepancies in this study. The fact that at the high-dose level the toxic symptoms observed in the mothers were severe and significant; including, bleeding (red stains around vulva) and one of the animals, MS 16, had the largest number of pups (19), makes the results questionable.

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